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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/646,628 | 08/22/2003 | Bernard Moss | NIH211.001C1 | 9682 |

26161 7590 09/13/2006

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| EXAMINER | |
|---|---|
| ZEMAN, ROBERT A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | |

DATE MAILED: 09/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/646,628 | MOSS ET AL. | |
| | Examiner | Art Unit | |
| | Robert A. Zeman | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 June 2006 and 23 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *31-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-18-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The amendment filed on 6-23-2006 is acknowledged. Claims 31 and 33-35 have been amended. Claims 36-38 have been added. Claims 31-38 are pending and currently under examination.

### *Information Disclosure Statement*

The information disclosure statement filed 7-18-2006 has been considered. An initialed copy is enclosed.

### *Objections Maintained*

### *Drawings*

The drawings filed on 8-22-2003 still are objected to. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the resolution of Figure 10 is such that one is unable to discern what is being presented. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance. It should be noted that Applicant did not address this objection in his response.

### *Specification*

The disclosure is still objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 19 for example). Applicant is required to check the

specification of all instances of hyperlinks and/or browser-executable code and them. See MPEP § 608.01. It should be noted that Applicant did not address this objection in his response.

The use of the trademarks Biojector and cytofix/cytoperm has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is required to check the specification for all instances of trademarks/tradenames being used. It should be noted that Applicant did not address this objection in his response.

***Claim Rejections Withdrawn***

The new matter rejection of claim 33 under 35 U.S.C. 112, first paragraph, based on the limitation "reducing reverse transcriptase activity" is withdrawn in light of the amendment thereto.

The new matter rejection of claim 34 under 35 U.S.C. 112, first paragraph, based on the limitation "reducing strand transfer activity" is withdrawn in light of the amendment thereto.

The new matter rejection of claim 35 under 35 U.S.C. 112, first paragraph, based on the limitation "reducing RNaseH activity" is withdrawn in light of the amendment thereto.

The rejection of claim 33 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "reverse transcriptase activity" is withdrawn in light

of the Applicant's arguments. Said term will be interpreted as meaning the activity of Pol when expressed by a wild type HIV virus.

The rejection of claim 34 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "strand transfer activity" is withdrawn in light of the Applicant's arguments. Said term will be interpreted as meaning the activity of Pol when expressed by a wild type HIV virus.

The rejection of claim 35 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "RNaseH activity" is withdrawn in light of the Applicant's arguments. Said term will be interpreted as meaning the activity of Pol when expressed by a wild type HIV virus.

The rejection of claims 31-35 under 35 U.S.C. 103(a) as being unpatentable over Kent et al. (Journal of Virology 1998, Vol. 72, No. 12, pages 10180-10188 – IDS) in view of Small et al. (U.S. Patent 5,676,950 – IDS) is withdrawn in light of the amendment thereto.

***Claim Rejections Maintained***

***35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Written Description Rejection***

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for essentially the reasons set forth in the previous Office action in the rejection of claims 33-35. The claim(s) still contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

**Applicant argues:**

1. The HIV genome and proteins expressed by HIV are extremely well studied and the genomes of many different HIV strains from a variety of clades have been sequenced in whole or in part (and were as of the priority date of the instant application).

2. HIV Pol has been extremely well studied.

3. The specification discloses that HIV sequences can be found in various sequence databases.

4. The HIV Sequences Compendium 2000 discloses nearly 100 HIV pol sequences from various clades that have been aligned with the HXB2 sequence providing a means to identify other pol variants that have a mutation that inhibits reverse transcriptase activity.

5. Said alignments identify domains associated with RNaseH activity and integrase activity.

6. Numerous mutations within HIV pol that inhibit reverse transcriptase activity, RNaseH activity or strand transfer activity (as demonstrated by the cited references) are known to those skilled in the art.

7. Given the large number of HIV sequences known to researchers, Applicant's description of mutations in HIV HXB2 pol that lead to reduced reverse transcriptase activity, reduced strand transfer activity or reduced RNaseH activity is sufficient to meet the written description requirement.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1-3, the rejection is based on which residues can be mutated to obtain an inhibition of a given activity. Other than the mutations of residues 185, 266, 478 of HIV-1 HXB2, the specification is silent as to what mutations would result in the desired reduction in a given pol activity. Hence, there is no correlation between structure and function as required to by the written description requirement. Moreover, with regard to claims 36-38 there is no baseline sequence recited so the recited residues have no clear-cut meaning.

With regard to Point 4-6, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The protein itself is required.

With regard to Point 7, the instant claims encompass all HIV strains (i.e. HIV-1, HIV-2, HIV-3 etc) while Applicant's arguments are based on HIV-1 only. Additionally, Applicant's arguments (and the Examples in the specification) are based on alignments using the HIV-1 HXB2 pol genome that is not part of the claims. Moreover, due to the high degree of variability in HIV genomes due to the 5-10% error rate associated with reverse transcription of the HIV RNA genome, one would not be able to

predict whether a given mutation would have the same effect in all HIV strains. Consequently, since there is no correlation between structure and the claimed function, it is deemed the written description requirement has not been met.

Finally, it is deemed that the baseline HIV sequences constitute essential material. The MPEP states:

> **608.01(p)**
> Newly filed applications obviously failing to disclose an invention with the clarity required are discussed in MPEP § 702.01.A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re Glass,* 492 F.2d 1228, 181 USPQ 31(CCPA 1974).
>
> An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, *Ex parte Schwarze*, 151 USPQ 426 (Bd. App. 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below.
> "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material **may not be** incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, **(2) non-patent publications**, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application.

As outlined previously, the specification discloses *gag, pol* and *env* genes and their incorporation into recombinant MVA viruses. However, the aforementioned claims are directed to sequences encoding proteins that have inhibited reverse transcriptase activity (claims 33 and 36), inhibited strand transfer activity (claims 34 and 37) or inhibited RNaseH activity (claims 35 and 38) encompassing mutated sequences. allelic variants, splice variants, sequences that have a recited degree of identity (similarity. homology), and so forth. None of these sequences meet the written description provision of 35 USC 112,

first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. **Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required**. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that:
...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2datl966.

> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel,* 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)
It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research.

### *New Claim Objections*

Claim 31 is objected to because of the following informalities: said claim contains an obvious typographical error. The term "cytoplamic" should read "cytoplasmic". Appropriate correction is required.

### *New Grounds of Rejection*

#### *35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 is rendered vague and indefinite by the use of the phrase "but lacking or all or part of the cytoplasmic domain of gp41". It is unclear what is meant to be engendered by said phrase. Consequently, it is impossible to determine the metes and bounds of the claimed invention.

#### *35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-385 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kent et al. (Journal of Virology 1998, Vol. 72, No. 12, pages 10180-10188 – IDS) in view of Small et al. (U.S. Patent 5,676,950 – IDS) and Gao et al. (Journal of Molecular Biology, 1998, Vol. 277, pages 559-572).

Kent et al. disclose methods of inducing CTL responses to HIV antigens utilizing methods consisting of priming with DNA and boosting with a recombinant Fowlpox virus wherein said DNA and recombinant Fowlpox encode (express) the *gag, pol* and *env* genes of HIV-1 (see abstract and Methods section on page 10181).

Kent et al. differs from the instant invention in that they don't disclose the use of a recombinant MVA virus.

Small et al. disclose the use of recombinant MVA viruses to immunize animals. Small et al. further disclose that a variety of heterologous genes or gene products can be inserted into the recombinant MVA (see column 5, lines 10-15). Moreover, Small et al. disclose that MVA constitutes a safe version of recombinant pox virus (see column 6, lines 1-38).

Gao et al. disclose that plasmids encoding HIV-1 IIIB Pol with mutations of residues 185, 266 and 478 have inhibited reverse transcriptase activity, strand transfer activity and RNaseH activity, respectively (see page.562 and 568-569).

Consequently, it would have been obvious to one of skill in the art to use the recombinant MVA viruses disclosed by Small et al. in the method disclosed by Kent et al. in order to take advantage of the increased safety associated with the use of MVA viruses in immunization protocols. One would have been equally motivated to use the mutated pol plasmids disclosed by Gao in order to further increase the safety as the resulting pol enzymes would be non-functional but still be immunogenic. One would have had a reasonable expectation of success since the recombinant MVA viruses have been disclosed by Kent et al. to be able to incorporate a multitude of heterologous genes.

***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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ROBERT A. ZEMAN
PRIMARY EXAMINER
September 7, 2006